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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTAGNA, ANGELA MARIE	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,502	GEDDES ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,12-16 and 18-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,12-16 and 18-27* is/are rejected.

7)☒ Claim(s) *5 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on January 3, 2008 is acknowledged. Claims 1, 4-10, 12-16, and 18-27 are currently pending. In the response, claims 1, 4, 8, 9, 15, 16, 18, 19, and 23 were amended, and claims 3, 4, 11, 17, and 38-49 were canceled.

It is noted that this application has been re-assigned to Examiner Angela Bertagna whose correspondence information is located at the conclusion of this Office Action. This Office Action contains new grounds of rejection that were not necessitated by the claim amendments in sections 3, 5, and 6. Any previously made rejections not reiterated below have been withdrawn. This Office Action is non-final.

Claim Objections

2. Claims 5 and 9 are objected to because of the following informalities:

(a) Claim 5 is grammatically incorrect. The word "is" should be replaced with "are".

(b) Claim 9 depends from a canceled claim – claim 2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-10, 12-15, 18, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: detecting *Bacillus anthracis* in a sample. This claim is drawn to "a method for detecting *Bacillus anthracis* in a sample", but it does not recite a detection step. Accordingly, this claim is missing an essential method step.

Claims 4-10 and 12-15 are also indefinite, since they depend from claim 1.

Claim 18 is indefinite, because it recites the limitation "the nucleotide sequence target pathogen" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Amendment of the claim to delete the words "nucleotide sequence" should overcome this rejection.

Claim 23 is indefinite, because it recites the limitation "the target pathogen nucleotide" in line 2. There is insufficient antecedent basis for this limitation in the claim. There is sufficient antecedent basis for "the target pathogen nucleotide sequence".

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 5, 9, 10, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh (US 5,814,516; cited previously) as evidenced by Lakowicz (US 2002/0160400 A1; cited previously), Doukas *et al.* (Proceedings of the National Academy of Sciences, USA (1984) 81: 4790-4794; newly cited), and Letuta *et al.* (Quantum Electronics (2001) 31(10): 925-928; newly cited) in view of Qi *et al.* (Applied and Environmental Microbiology (2001) 67(8): 3720-3727; newly cited).

These claims are drawn to a method for detecting *Bacillus anthracis* in a sample. The method comprises hybridizing a sample suspected of containing *Bacillus anthracis* nucleic acids to an oligonucleotide immobilized on a layer of immobilized metal particles followed by hybridizing a fluorescently labeled oligonucleotide to the hybridized duplex.

Regarding claim 1, Vo-Dinh teaches a method for detecting a pathogen in a sample comprising:

(a) providing a system comprising: a layer of immobilized metal particles positioned on a surface substrate, wherein the immobilized metal particles have a captured nucleotide sequence

probe complementary to a first portion of a nucleotide sequence in the target pathogen attached thereto (see column 3, lines 48-55, column 6, lines 5-41, column 7, line 18 – column 8, line 22, and column 11, lines 7-21)

(b) contacting the sample and the captured nucleotide sequence probe, thereby binding any pathogen nucleic acids that are complementary to the captured nucleotide sequence probe (column 3, lines 61-65)

(c) contacting any bound pathogen nucleic acids with a free nucleotide sequence probe, wherein the free nucleotide sequence probe probe has an affinity for a second portion of the pathogen nucleic acid and has a fluorophore attached thereto (column 3, line 55 - column 4, line 4; column 6, lines 62-65 teach that the label is a fluorophore).

Further regarding claim 1, as evidenced by Lakowicz at paragraphs 70-75, 81, and 84, when the fluorescently labeled free nucleotide sequence probe taught by Vo-Dinh binds to the pathogen nucleic acid which is captured via hybridization to the oligonucleotide immobilized on metal particles, the fluorophore is inherently positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission when excited by an irradiating source.

Regarding claim 5, Vo-Dinh teaches that the metal particles are silver or gold (see column 8, lines 15-18 and co1umn 12, lines 29-30).

Regarding claim 9, Vo-Dinh teaches binding the captured and free nucleotide sequence probes to the pathogen nucleic acid under highly stringent hybridization conditions (co1umn 10, lines 50-55).

Regarding claim 10, Vo-Dinh teaches that the irradiating source uses a 1-photon excitation means (co1umn 9, lines 8-15).

Regarding claim 12, as evidenced by Doukas at page 4791, column 2, the erythosin taught by Vo-Dinh at column 6, line 65 has a low quantum yield.

Regarding claim 13, as evidenced by Letuta at page 927 (see Figure 3), the erythrosin taught by Vo-Dinh at column 6, line 65 can undergo two-photon excitation.

Vo-Dinh teaches using the method to detect a number of different bacterial and viral pathogens (column 6, lines 5-41). However, Vo-Dinh does not teach using the method to detect *Bacillus anthracis* as required by claim 1.

Qi teaches a method for detecting *Bacillus anthracis* in a sample using PCR. Regarding this pathogen, Qi stated, "*Bacillus anthracis* is a causal agent of anthrax, a serious and often fatal infection of livestock and humans. It is considered one of the most effective biological weapons of mass destruction because of its highly pathogenic nature and spore-forming capability and has attracted attention due to its potential use as a biological warfare agent (page 3720, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to use the method taught by Vo-Dinh for the detection of *Bacillus anthracis*. An ordinary artisan would have been motivated to do so, since Qi taught that this pathogen was "one of the most effective biological weapons of mass destruction (page 3720, column 1)." An ordinary artisan would have had a reasonable expectation of success in designing captured and free nucleotide sequence probes to detect Bacillus anthracis, since Qi taught that the complete *Bacillus anthracis rpoB* gene sequence was publicly available and successfully designed nucleic acid primers and probes from this sequence (pages 3722-3724). Thus, the methods of claims 1,

5, 9, 10, 12, and 13 are *prima facie* obvious over Vo-Dinh as evidenced by Lakowicz, Doukas, and Letuta in view of Qi.

6. Claims 1, 4-10, 12-16, and 18-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao *et al.* (Science (2002) 297: 1536-1540; cited previously) as evidenced by Malicka *et al.* (Biopolymers (2003) 72(2): 96-104; newly cited) and Lukomska *et al.* (Biochemical and Biophysical Research Communications (2005) 328: 78-84; newly cited) in view of Lakowicz (US 2002/0160400 A1; cited previously and hereafter "Lakowicz I") and further in view of Lakowicz *et al.* (Biochemical and Biophysical Research Communications (2001) 286: 875-879; cited on an IDS and hereafter "Lakowicz II").

The applied reference (Lakowicz I) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome

by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

These claims are drawn to a method for detecting *Bacillus anthracis* in a sample. The method comprises hybridizing a sample suspected of containing *Bacillus anthracis* nucleic acids to an oligonucleotide immobilized on a layer of immobilized metal particles followed by hybridizing a fluorescently labeled oligonucleotide to the hybridized duplex.

Cao teaches a sandwich assay for detecting target nucleic acid from a pathogen in a sample (see abstract and Scheme 1 on page 1537).

Regarding claims 1 and 16, the method of Cao comprises:

(a) providing surface-immobilized capture nucleotide sequence probe complementary to a first portion of a nucleotide sequence in the pathogen (see Scheme 1 and page 1537, column 1, paragraph 2)

(b) contacting the sample and the capture nucleotide sequence probe, thereby binding any pathogen nucleic acids that are complementary to the capture nucleotide sequence probe (see Scheme 1 and page 1537, column 1, paragraph 2)

(c) contacting any bound pathogen nucleic acids with a free nucleotide sequence probe, wherein the free nucleotide sequence probe has an affinity for a second portion of the pathogen nucleic acid and has a fluorophore attached thereto (see Scheme 1 and page 1537, column 1, paragraph 2)

(d) identifying the pathogen using surface enhanced Raman spectroscopy (see Scheme 1 and pages 1537-1538).

Further regarding claim 1 and also regarding claim 18, Cao teaches using the method to detect *Bacillus anthracis* (page 1538, column 1).

Regarding claim 8, Cao teaches covalent immobilization of the capture nucleotide sequence probe to the surface (see Scheme 1 and page 1537, column 1).

Regarding claims 9 and 23, Cao teaches binding the capture and free nucleotide sequence probes to the pathogen nucleic acid under highly stringent hybridization conditions (page 1539).

Regarding claims 12 and 25, as evidenced by Malicka at page 100, column 1, the Cy3 fluorophore taught by Cao has a low quantum yield.

Regarding claims 13 and 26, as evidenced by Lukomska at pages 78-80, the Cy3 fluorophore taught by Cao can undergo two-photon excitation.

Cao does not teach that the immobilized capture probes are immobilized to metal particles or a metal layer on a substrate as required by claims 1 and 16, respectively. Also, Cao teaches detection using Raman spectroscopy rather than fluorescence spectroscopy. Finally, Cao does not teach that the free nucleotide sequence probe further comprises a metal colloid attached thereto for sandwiching the fluorophore between the metal colloid and the metallized substrate as required by claims 15 and 16.

Lakowicz I teaches a method for increasing the fluorescence of a fluorophore using metal particles (see abstract and paragraph 13).

Regarding claims 1, 15, and 16, Lakowicz I teaches that the fluorescence intensity of a fluorophore conjugated to a biomoleucle, such as DNA or RNA, can be increased at least 80 to 140 fold by positioning the fluorophore near a metal particle (paragraphs 13, 18, 71, and 84). Lakowicz I provides an example of this increase in fluorescence intensity in Figure 3, Figure 8,

Figure 19, and paragraphs 114-116, 122, and 131-132, where the intensity of a fluorophore is increased by sandwiching between silver island films. Lakowicz I further teaches that colloids may be substituted for the silver island films (paragraph 71).

Regarding claims 4 and 19, Lakowicz I teaches that the distance between the fluorophore and the metal particle should be optimized and separation distances between about 50 and about 2000 Angstroms, about 50 to about 200 Angstroms, and about 50 to about 300 Angstroms are particularly useful (paragraphs 71-72).

Regarding claims 5 and 20, Lakowicz I teaches the use of silver particles (paragraph 71) or gold particles (paragraph 70).

Regarding claims 6, 7, 21, and 22, Lakowicz I teaches detecting fluorescence emission using a detection device comprising a spectrometer (paragraph 76) or a fluorescent scanner (paragraph 91).

Regarding claim 8, Lakowicz I teaches covalent immobilization to the metal particles (paragraph 72).

Regarding claims 10 and 24, Lakowicz I teaches irradiating the fluorophore using a single photon (paragraph 149) or a two-photon excitation means (paragraphs 100 and 147).

Regarding claims 12-14 and 25-27, Lakowicz I teaches using a fluorophore with a low quantum yield, such as Rhodamine B, rose bengal, or fluorescein isothiocyanate (paragraphs 64, 66, and 84). Lakowicz I teaches fluorophores with a low quantum yield only fluoresce when they are adjacent to a metal particle (paragraph 105). Lakowicz I further teaches that these fluorophores can undergo two-photon excitation (paragraph 147).

Lakowicz II teaches that the intrinsic fluorescence from DNA and the extrinsic fluorescence from a fluorophore conjugated to a DNA molecule can be enhanced by sandwiching the fluorophore between metal particles (see abstract, page 875, and page 877, and Figure 3). Lakowicz further teaches that the fluorescence enhancement in the presence of metal particles is analogous to surface-enhanced Raman spectroscopy (page 878).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Lakowicz I and Lakowicz II to the method taught by Cao. An ordinary artisan would have been motivated to sandwich the Cy3 fluorophore between metal particles, such as a metal colloid, and measure fluorescence emission from the fluorophore, as taught by Lakowicz I, since Lakowicz I and Lakowicz II taught that the fluorescence signal could be enhanced by sandwiching a fluorophore between metal particles (see above). Since Lakowicz II taught that fluorescence enhancement by metal particles was analogous to surface-enhanced Raman spectroscopy (page 878) and since the methods of Lakowicz I and Lakowicz II were directed to enhancing the fluorescence of an extrinsic fluorophore conjugated to a nucleic acid (see above), an ordinary artisan would have been motivated to utilize either of these analogous detection methods to detect *Bacillus anthracis* in the method of Cao with a reasonable expectation of success. Thus, the methods of claims 1, 4-10, 12-16, and 18-27 are *prima facie* obvious over Cao as evidenced by Malicka and Lukomska in view of Lakowicz I and further in view of Lakowicz II.

Response to Arguments

7. It is noted that all of the previously made rejections have been withdrawn. Therefore, Applicant's arguments filed on January 3, 2008 regarding these rejections have been considered, but they are moot in view of the new grounds of rejection presented above.

Conclusion

8. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amb

/Cynthia Wilder/
Patent Examiner
Art Unit 1637